

Synthesis and evaluation of antimicrobial activity of cyclic imides derived from phthalic and succinic anhydrides

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Abstract

Cyclic imides are a group of compounds which have valuable biological properties including cytotoxic, anti-inflammatory, antibacterial and antifungal activities. In this study, succinic and phthalic anhydrides were treated with glycinamide in pyridine to yield the corresponding amic acids. These amic acids underwent ring closure with acetic anhydride and anhydrous sodium acetate to form cyclic imides. In another procedure, succinic and phthalic anhydrides upon reaction with 2-amino-benzylamine in pyridine gave the corresponding cyclic imides. The imides were screened for their antimicrobial activities against three types of bacteria and one type of fungi. Phthalimide derived from benzylamine exhibited remarkable antimicrobial activity against *E. coli*.

Keywords: Cyclic imides; Glycinamide; 2-Amino-benzylamine; Antimicrobial

INTRODUCTION

Cyclic imides and their N-derivatives as an important class of organic compounds, contain bis-amide linkages with a general structure of [-CO-N(R)-CO-]. Their hydrophobicity and neutral structures enable them to easily cross biological membranes (1-6). These molecules are reported to exhibit valuable biological effects including antifungal (7-9), antibacterial (10-14), anticancer, apoptosis induction (6,15), anti-inflammatory (16), androgen receptor antagonists (3), anxiolytic, and anticonvulsant (2,3). Structure activity relationship studies of these systems in some literatures revealed that incorporation of heterocyclic moiety in the imide portion or linkage with nitrogen improve their anti-inflammatory and antitumor activities. Antitubercular activity was reported for cyclic imides with a *para*-sulphonamide group (1,3). These molecules could be used as building blocks in the synthesis of natural products such as coumarins and atacoumarins and also as core structures in the design and

synthesis of peptidomimetics (1,3). The alkaloid phyllanthimide isolated from leaves of *Phyllanthus sellowianus* (euphorbiaceae) has been used as a precursor for the synthesis of some analogs of cyclic imides (1). Some examples with cyclic imide structure are shown in Fig 1. Gayoso, *et al.* have reported antifungal effectiveness of 3,4-dichloro-N-phenyl-alkyle-maleimide derivatives. Compounds 3, 4-dichloro-N-phenyl-methyl-maleimide and 3,4-dichloro-N-phenyl-propilmaleimide displayed antifungal activities with MIC of 100 µg/mL against fungal strains (7). Sultana, *et al.* succeeded to synthesize 2-(2-methoxyphenyl)-1*H*-isoindole-1, 3(2*H*)-dione ligand and some of the metal complexes by using a simple method. Synthesized complexes exhibited improved antibacterial effects in comparison to their parent ligand (14).

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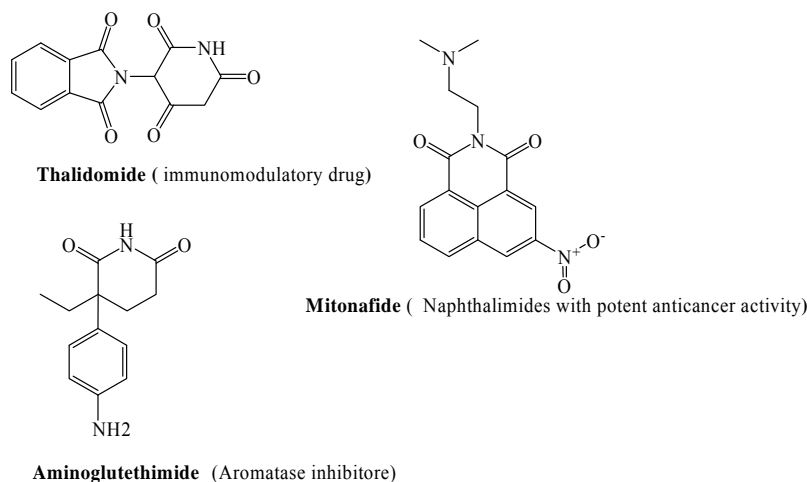


Fig. 1. Some dugs with cyclic imide structure.

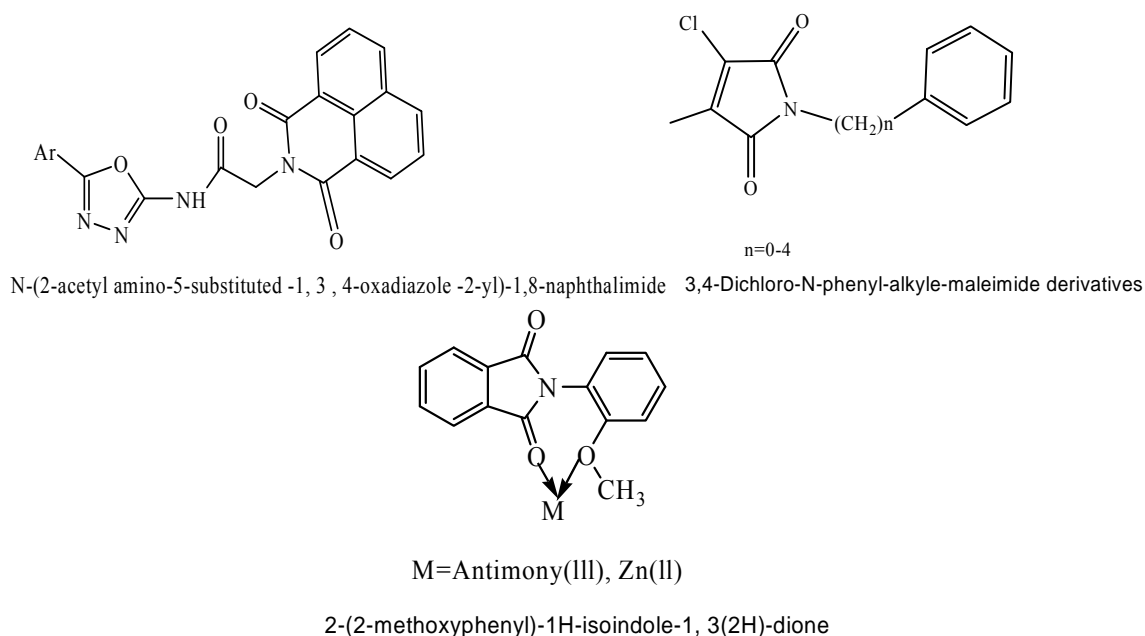


Fig. 2. Cyclic imides with antimicrobial activity.

Al-Azzawi, *et al.* synthesized N-(2-acetyl amino-5-substituted -1, 3, 4-oxadiazole -2-yl)-1,8-naphthalimide derivatives with remarkable antimicrobial activity against *E. coli* (17) Fig. 2.

There are some procedures available for cyclic imides synthesis, such as the dehydrative condensation of a cyclic anhydride and amine (2), the use of expensive catalysts (18), and microwave synthesis (9). In this study, the first method, with some modifications was used to prepare the compounds.

MATERIALS AND METHODS

Instrumentation

Melting points were determined in open capillaries using electrothermal 9200 melting point apparatus (UK) (England) and are uncorrected. IR (KBr discs) was recorded with a WQF-510 FT-IR spectrophotometer (China). ¹H-NMR spectra were recorded on Bruker 400 MHz spectrometers (Germany) using TMS as an internal standard and either DMSO-d₆ or CDCl₃ as solvents. Mass spectra were

recorded on Finnigan TSQ-70 Mass spectrometer (United States). All chemicals were purchased from Merck Company (Germany).

Amic acids synthesis procedures from (2-amino acetamide or glycineamide) (A₁G, A₂G, A₃G)

Phthalic, succinic and maleic anhydride (0.01 mol) and glycineamide (0.01 mol) were transferred separately to round bottom flasks and then freshly distilled and dried pyridine was added slowly while shaking. The mixture was heated under refluxed for 5 h. Excess of pyridine was distilled off under reduced pressure, and then methanol was added to residue to obtain crystalline solids (Fig. 3).

Preparation of phthalimide

Obtained amic acid of phthalic anhydride (0.01 mol) in 20 mL acetic anhydride and 0.001 mol anhydrous sodium acetate was refluxed with stirring for 4 h (4,12,17). The

resulted homogenous solution was cooled to room temperature and then poured into excess cold water with vigorous stirring. The obtained precipitate was filtered, washed with distilled water, dried and finally purified by column chromatography on silica gel using CHCl₃-MeOH (49:1) as eluent to give FA₁G and FA₁GAc (Fig. 3).

Preparation of succinimide

Obtained amic acid of succinic anhydride (0.01 mol) was dissolved in acetic anhydride (20 mL) and anhydrous sodium acetate (0.001 mol) and refluxed with stirring for 4 h (4, 12, 17). The solvent was removed by distillation under reduced pressure.

The obtained residue was dissolved in chloroform, then solvent was removed by distillation under reduced pressure. The obtained product was purified by column chromatography on silica gel using CHCl₃-MeOH (49:1) as eluent to afford FA₃G (Fig. 3).

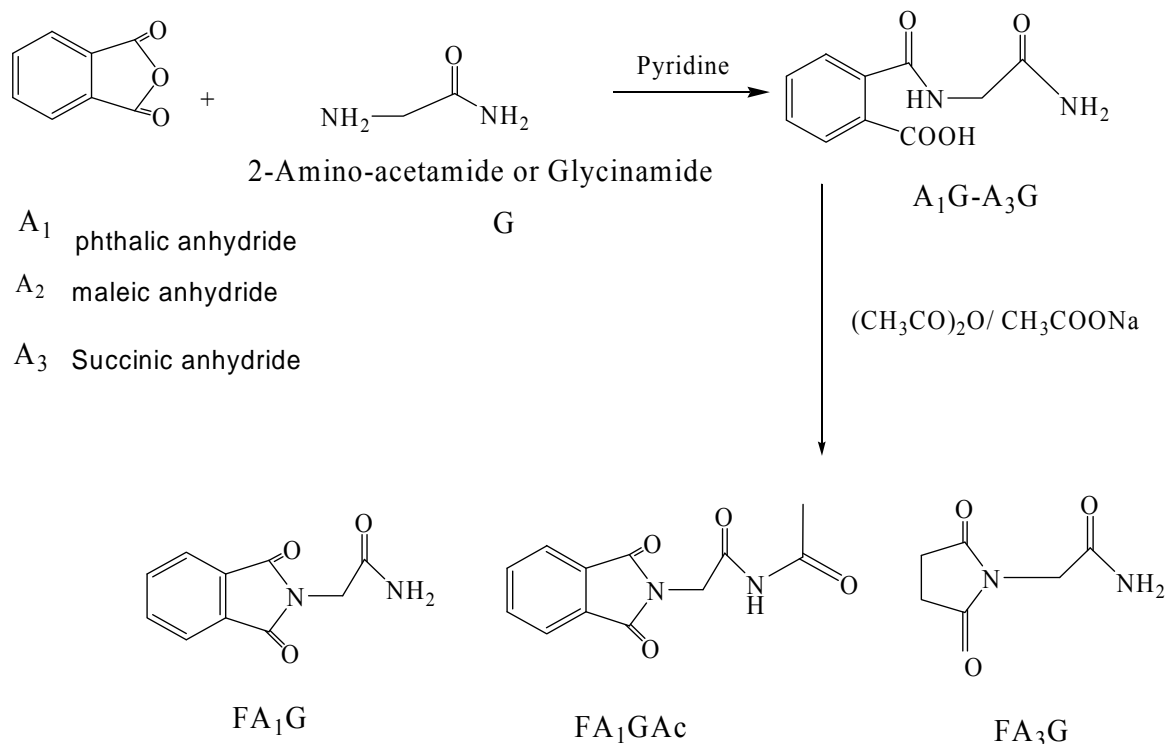


Fig. 3. Synthesis of cyclic imides of (2-amino acetamide or glycineamide).

Preparation of cyclic imides of (2-amino benzylamine)

Preparation of phthalimide

Phthalic anhydride (0.01 mol) and 2-aminobenzylamine (0.01 mol) were placed in a round bottom flask and freshly distilled and dried pyridine was then added slowly while shaking. The mixture was heated under reflux for 5 h. The solvent was distilled off under reduced pressure. Obtained residue was dissolved in ethyl acetate and purified by column chromatography to afford **A₁B** (Fig. 4).

Preparation of succinimide

Succinic anhydride (0.01 mol) and 2-aminobenzylamine (0.01 mol) were put in a round bottom flask and freshly distilled and dried pyridine was then added slowly while shaking. The mixture was heated under reflux for 5 h. Excess of pyridine was distilled off under reduced pressure; then ethanol and water were added to the residue to obtain light brown precipitant **A₃B** (Fig. 4).

Antimicrobial activity

Microorganisms were obtained from Persian Type Culture Collection (PTCC). *Staphylococcus aureus* PTCC1337 as Gram-

positive, *Escherichia coli*, PTCC 1338 and *Pseudomonas aeruginosa*, PTCC1074, as Gram-negative bacteria and *Candida albicans* PTCC, 5027 as fungus. Mueller Hinton Agar, Mueller Hinton Broth and Sabouraud Dextrose Agar were purchased from Merck (Germany) Roswell Park Memorial Institute (RPMI)-1640 culture medium was procured from Gibco, USA.

Microplate alamar blue assay (MABA) for antimicrobial evaluation

The inocula of bacterial and fungal strains (1.5×10^8 CFU/mL) were prepared from Mueller Hinton Agar and Sabouraud Dextrose Agar cultures respectively. Prepared suspensions of bacteria were adjusted to 0.5 Mc Farland standard turbidity and the fungal suspensions turbidity was measured spectrometrically at 580 nm. Finally, prepared inoculum density for bacterial and fungal strains were equal to 1.0×10^5 CFU/mL and 1.0×10^6 CFU/mL respectively. The synthesized compounds were dissolved in DMSO (0.5 mL) and diluted with water up to 1 mL to obtain concentration of 5120 μ g/mL as the stock solution. The stock solution was serially diluted to give concentrations of 2560 to 80 μ g/mL.

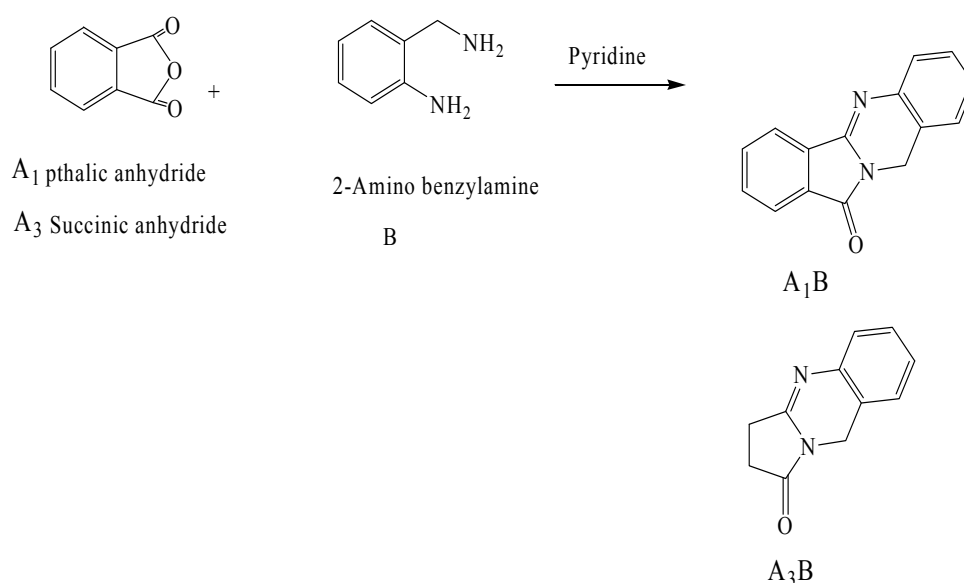


Fig. 4. Synthesis of cyclic imides of (2-amino benzylamine).

Mueller Hinton Broth was used as medium for bacterial growth and RPMI 1640 was used as medium for fungal growth. 20 μ L of bacterial suspension was distributed in all 96 wells of microplate.

Then 20 μ L of each concentration of the compounds were added to wells with the exception of those wells acting as positive control (containing standard antibiotic) and growth control (containing culture media without testing materials). After adding alamar blue (20 μ L) to all of 96 wells the total volume in each well was adjusted to 200 μ L using culture medium.

The final concentrations of the compounds in the wells were 512, 256, 32, 16, and 8 μ g/mL. After incubation, the MIC was defined as the lowest concentration, which prevented a color change from blue to pink. The test was carried out in triplicates.

Following the MIC test, the content of each well that showed no growth was removed and spread onto a plate containing appropriate medium for bacteria and fungi to determine MBC (minimum bactericidal concentration) and MFC (minimum fungicidal concentration) results.

Pharmacokinetic parameters estimation using Swiss ADME

Absorption and Lipinski's "rule of five" parameters of the compound **A₁B** which exhibited remarkable antimicrobial activity were calculated using online Swiss ADME. Lipinski's "rule of five" including molecular weight (MW), number of H-bond donors (NHBD), number of H-bond acceptors (NHBA) and log P are widely used as a filter for drug-like properties (19).

RESULTS

4-(2-amino-2-oxoethylamino)-4-oxobut-2-enoic acid (**A₂G**)

Brown powder, yield: 40%, m.p.: 244-246 °C, MS (m/z, %): 172 (100) for C₆H₈N₂O₄, M.W.: 172.14, IR (KBr, cm⁻¹), 3420, 3324 (NH₂), 3197 (NH), 1702, 1657 (C=O). ¹H-NMR δ _H (400 MHz; DMSO), 8.70 (1H, t, *J* = 4 Hz, NH), 7.4, 7.04 (2H, s, NH₂), 6.98 (1H, d,

J = 15.2 Hz, OH-CO-CH=CH-CONH-CH₂-CO-NH₂), 6.50 (1H, d, *J* = 15.6 Hz, OH-CO-CH=CH-CONH-CH₂-CO-NH₂), 3.73 (2H, d, *J* = 4 Hz, OH-CO-CH=CH-CONH-CH₂-CO-NH₂).

4-(2-amino-2-oxoethylamino)-4-oxobutanoic acid (**A₃G**)

White powder, yield: 50%. m.p.: 155-157 °C, MS (m/z, %): 174 (100) for C₆H₁₀N₂O₄, M.W.: 174.15, IR (KBr, cm⁻¹), 3422, 3332 (NH₂), 1718, 1651 (C=O). ¹H-NMR (400 MHz, DMSO) δ : 12.1 (1H, OH), 8.11 (1H, t, *J* = 4 Hz, NH), 7.1, 7.03 (2H, s, NH₂), 3.6 (2H, d, *J* = 4 Hz, OH-CO-CH₂-CH₂-CONH-CH₂-CO-NH₂), 2.43 (2H, t, *J* = 8 Hz, OH-CO-CH₂-CH₂-CONH-CH₂-CO-NH₂), 2.37 (2H, t, *J* = 8 Hz, OH-CO-CH₂-CH₂-CONH-CH₂-CO-NH₂).

2-(1, 3-dioxoisindolin-2-yl) acetamide (**FA₁G**)

White powder, yield: 40% , m.p.: 255-256 °C (lit. 255-257 °C), MS (m/z, %): 204 (6) for C₁₀H₈N₂O₃, M.W.: 204.18, IR (KBr, cm⁻¹), 3413, 3321 (NH₂), 3066 (CH, Ar), 1770, 1682 (C=O) ¹H-NMR (400 MHz, DMSO) δ : 7.88 (2H, dd, *J* = 6 Hz, *J* = 2.8 Hz, CO-C=CH-CH=CH-CH=C-CO), 7.86 (2H, dt, *J* = 6 Hz, *J* = 2.8 Hz, CO-C=CH-CH=CH-CH=C-CO), 4.13 (2H, s, CH₂), 7.68, 7.23 (NH₂, s).

N-[2-(1, 3-dioxoisindolin-2-yl) acetyl]-acetamide (**FA₁GAc**)

White powder, yield: 10%, m.p.: 263-265 °C, C₁₂H₁₀N₂O₄, M.W.: 246, IR (KBr, cm⁻¹), 3237 (NH), 3097 (CH, Ar), 1783, 1640, 1690 (C=O), ¹H-NMR (400 MHz, CDCl₃) δ : 8.35, (NH, s), 7.89 (2H, dd, *J* = 5.2 Hz, *J* = 3.2 Hz, CO-C=CH-CH=CH-CH=C-CO), 7.75 (2H, dt, *J* = 5.2 Hz, *J* = 3.2 Hz, CO-C=CH-CH=CH-CH=C-CO), 4.81 (2H, s, CH₂), 2.27 (3H, s, CH₃).

2-(2, 5-dioxopyrrolidin-1-yl) actamide (**FA₃G**)

White powder, yield: 23 %, m.p.: 165-167.5 °C, MS (m/z, %), 156 (6) for C₆H₈N₂O₃, M.W.: 156, IR (KBr, cm⁻¹), 3413, 3321 (NH₂), 1770, 1682 (C=O) ¹H-NMR (400 MHz, CDCl₃) δ : 5.51 (2H, s, NH₂), 4.14 (2H, s, CH₂), 2.75 (4H, s, O=C-CH₂-CH₂-C=O).

Isoindolo[1,2-b]quinazolin-12(10H)-one (A₁B)

Yellow powder, yield: 30%, m.p.: 174-176 °C (lit. 175-177 °C), MS (m/z, %): 234 (6) for C₁₅H₁₀N₂O, M.W.: 234, IR (KBr, cm⁻¹), 1650 (C=N), 1601 (C=C), ¹H-NMR (400 MHz, CDCl₃) δ: 8.08 (1H, d, *J* = 7.2 Hz, N-CO-C=CH-CH=CH-CH=C-C=N), 7.92 (1H, d, *J* = 8 Hz, N-CO-C=CH-CH=CH-CH=C-C=N), 7.67-7.74 (2H, t, *J* = 8 Hz, N-CO-C=CH-CH=CH-CH=C-C=N), 7.51 (1H, d, *J* = 8 Hz, N-C=CH-CH=CH-CH=C-CH₂), 7.34 (1H, t, *J* = 8 Hz, N-C=CH-CH=CH-CH=C-CH₂), 7.25 (1H, t, *J* = 8 Hz, N-C=CH-CH=CH-CH=C-CH₂), 7.21 (1H, d, *J* = 8 Hz, N-C=CH-CH=CH-CH=C-CH₂), 5.01 (2H, s, CH₂).

2, 3-dihydropyrrolo [2, 1-b]quinazoline-1 (9H)-one (A₃B)

Light brown powder, yield: 30%, m.p.: 165-166 °C (lit. 185-187 °C), C₁₁H₁₀N₂O,

M.W.: 186, IR (KBr, cm⁻¹), 3026, 3066 (CH, Ar), 1685 (C=N), 1662 (C=O), ¹H-NMR (400 MHz, CDCl₃) δ: 7.23-7.06 (4H, m, Ar-H), 4.85 (2H, s, CH₂), 2.94 (2H, t, *J* = 4 Hz, CH₂-C=O), 2.68 (2H, t, *J* = 4 Hz, CH₂-C=N).

Results of online Swiss ADME software

Absorption and Lipinski's "rule of five" properties of the compound A₁B are shown in Table 1.

Antimicrobial results

The MICs of all tested compounds were evaluated at concentrations 8 to 512 µg/mL. Compound A₁B showed significant inhibition at 16 µg/mL concentration against *E. coli* as a gram-negative bacteria.

Results of MIC, MBC and MFC are depicted in Tables 2 and 3.

Table 1. Absorption and Lipinski parameters of A₁B.

Absorption	Log P _{o/w}	H-bond acceptors	H-bond donors	Molecular weight	Lipinski
High	2.54	2	0	234	yes

Log P (Partition coefficient).

Table 2. Minimum inhibitory concentrations of synthesized compounds against bacteria and fungi.

Substance	Gram-negative bacteria MIC (µg/mL)		Gram-positive bacteria MIC (µg/mL)	Fungus MIC (µg/mL)
	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>C. albicans</i>
A ₁ B	16	512	512	512
A ₃ B	-	512	-	512
A ₂ G (open ring)	-	-	-	--
A ₃ G (open ring)	-	512	-	512
FA ₁ G	-	-	-	512
FA ₁ GAc	-	-	-	512
FA ₃ G	-	512	-	512

Ciprofloxacin, 50 (µg/mL) as standard antibacterial agent; Ketoconazole 50 (µg/mL) as standard antifungal agent; MIC, Minimum inhibitory concentration.

Table 3. Minimum fungicidal and minimum bactericidal concentrations of synthesized compounds against bacteria and fungi.

Substances	Gram negative bacteria MBC (µg/mL)		Gram positive bacteria MBC (µg/mL)	Fungus MFC (µg/mL)
	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>C. albicans</i>
A ₁ B	256	-	-	-
A ₃ B	NA	-	NA	-
A ₂ G (open ring)	NA	NA	NA	NA
A ₃ G (open ring)	NA	-	NA	-
FA ₁ G	NA	NA	NA	-
FA ₁ GAc	NA	NA	NA	-
FA ₃ G	NA	-	NA	-

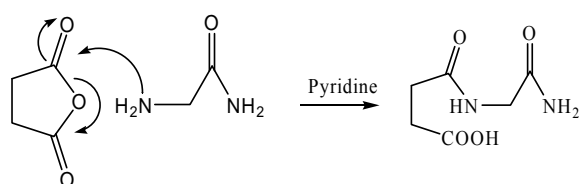
MFC, minimum fungicidal concentration; MBC, minimum bactericidal concentration; NA, not applicable.

DISCUSSION

In the first step to produce cyclic imides, the reaction was proceed via nucleophilic attack of amino group ($\text{NH}_2\text{-CH}_2$) of glycineamide on one carbonyl group in cyclic anhydrides to yield corresponding amic acids. Treatment of amic acids with acetic anhydride gave the cyclic imides through dehydrative cyclization mechanism (Fig. 5). In another procedure, benzylic amine of 2-amino-

benzylamine acted as a nucleophile and attacked the carbonyl group of the cyclic anhydride which resulted in the ring opening and subsequently forming the cyclic imides. $\text{NH}_2\text{-ph}$ group of 2-amino-benzylamine attacked the carbonyl group of cyclic imide and the second ring closure was achieved simultaneously to produce cyclic imide (Fig. 6). Reaction between maleic anhydride and the same amines could not produced cyclic imides by these methods.

Step 1:



Step 2:

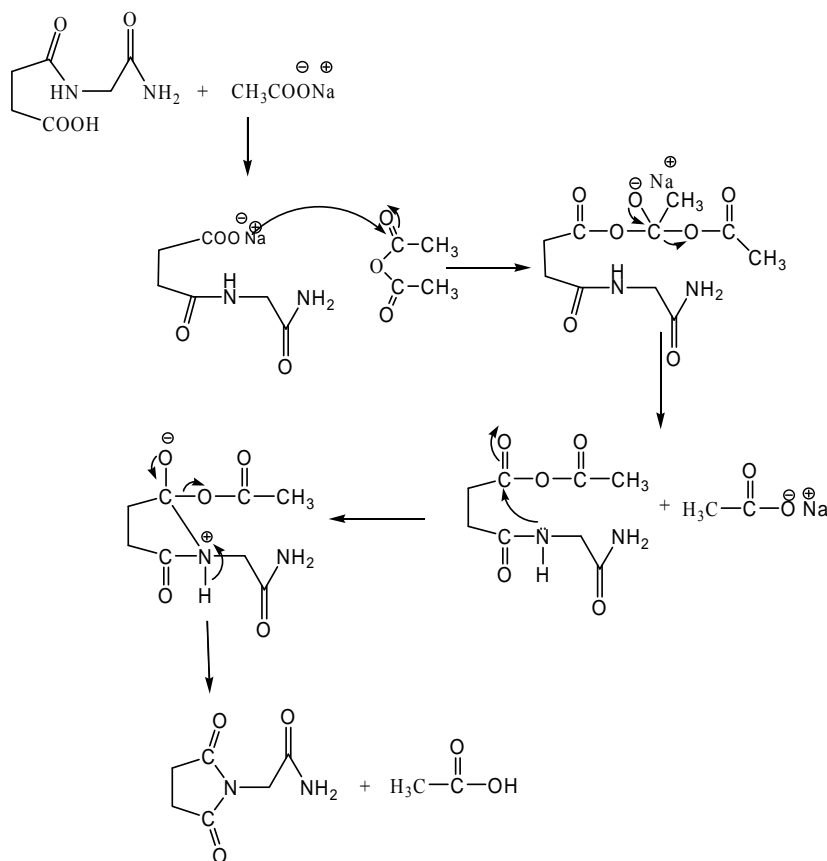


Fig. 5. Proposed mechanism for the synthesis of compound.

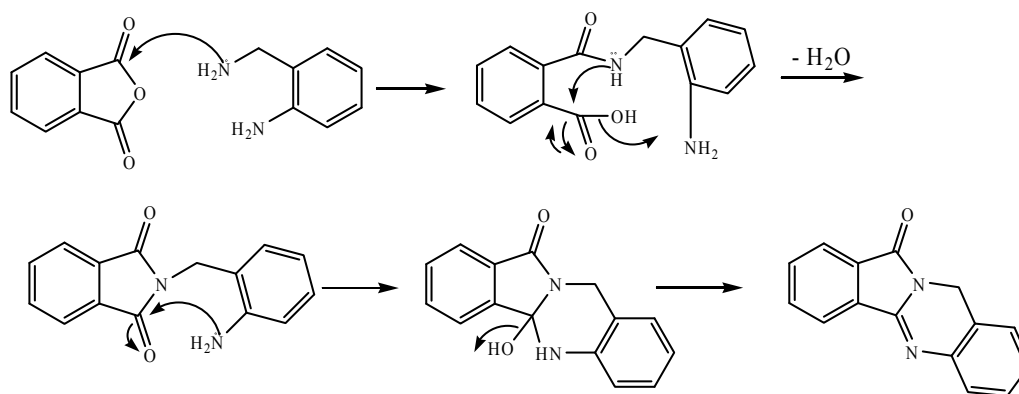


Fig. 6. Proposed mechanism for the synthesis of compound **A₁B**.

IR spectra of the prepared imides (**FA₁G** and **FA₃G**) showed disappearance of absorption bands which belong to (O-H) carboxylic and (N-H). This can be clear proof for the synthesis of cyclic imides.

According to the antimicrobial evaluations, phthalimide derived from benzylamine (**A₁B**) exhibited remarkable antimicrobial activity against *E.coli*. Phthalimide, isoindoline-1,3-dione have shown a wide array of pharmacological activities. Schiff base, azetidinone and acetyl oxadiazole derivatives of this cyclic imide with high antibacterial activities were synthesized and reported by Azzawi, *et al.* (12).

Literature survey revealed that naphthalimides, one type of cyclic imides with strong hydrophobicity, have remarkable antimicrobial activities (4,20-22). Relative similarity of this compound (**A₁B**) with naphthalimides, can be responsible for its antibacterial activity. Sortino, *et al.* demonstrated that N-phenyl- and N-phenylalkylmaleimides can display antifungal activities with their intact maleimide ring and opening of the maleimide ring would lead to the loss of antifungal activity (7,8). In our study, cyclic imides derived from succinic anhydride, **A₃G** (opened derivative) or **FA₃G** (intact ring), did not show significant activity against tested microorganisms.

Lipinski's "rule of five" explains four physicochemical properties for orally active drugs. In this regard, most molecules with acceptable membrane permeability, exhibit hydrogen bond donors (OH, NH) of less than 5, hydrogen bond acceptor of less than 10,

molecular weight under 500 g/mol and partition coefficient (log *P*) less than 5. Any value greater than these ranges is considered as a violation. The number of violations less than 4 is acceptable for drug-like molecule. Compound **A₁B** can, therefore, be considered as a drug-like molecule according to Lipinski's "rule of five".

CONCLUSION

Compound **A₁B** with significant efficacy against *E. coli* at 16 µg/mL concentration and acceptable Lipinski's parameters can be regarded as a drug likeness molecule. The activity of this compound can be associated with its stability as well as relatively lipophilic structure. Other compounds showed weak activities against tested microorganisms.

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